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(54) Title: METHOD OF PREPARATION OF INCLUSION COMPOUNDS OF NIMESULIDE WITH CYCLODEXTRINS

(57) Abstract

A method for the preparation of inclusion compounds of nimesulide with cyclodextrins, which consists in subjecting a solid mixture, an aqueous solution or a homogeneous slurry of nimesulide and water-soluble cyclodextrins to co-milling, to spray-drying or to kneading respectively, is described.

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METHOD OF PREPARATION OF INCLUSION COMPOUNDS OF NIMESULIDE WITH CYCLODEXTRINS

The present invention relates to a new method for the preparation of inclusion compounds of nimesulide with cyclodextrins.

The inclusion compound of nimesulide with cyclodextrins and the relevant methods of preparation are already described in the Italian patent application No. 20393 A/90 as compound endowed with analgesic and antiinflammatory activity, having a good water solubility and a more efficient and rapid absorption in comparison with the uncomplexed nimesulide.

The methods of preparation of the inclusion compound of nimesulide with cyclodextrins, described in the above mentioned Italian patent application, include the coprecipitation of the inclusion compound from an organic solution of nimesulide mixed with an aqueous solution of cyclodextrin, or the neutralization of the aqueous solution of cyclodextrins, the solubilization of nimesulide and isolation of the inclusion compound, or the isolation from saturated aqueous solution of the inclusion compound of nimesulide with cyclodextrins.

By these methods, the inclusion compound can be isolated by filtration, freeze-drying or evaporation under reduced pressure.

These methods are industrially not much applicable for great amounts of aqueous or organic solution to be used, requiring a considerable expenditure of time and expensive processes when they must be removed, besides showing obvious implications at environmental level.

These procedures require long time and multistage processing including solubilization, initial reaction, recrystallization, filtration, washing and drying. Some of these methods foresee the use of an organic solvent whose residues in the inclusion compound may be difficult to eliminate completely or may cause environmental problems.

The present invention relates to an one-step process for the preparation of the inclusion compounds of nimesulide with water-soluble cyclodextrins.

The method of the invention consists in subjecting a solid mixture, an aqueous solution or an homogeneous slurry of nimesulide and water-soluble cyclodextrins to co-milling, to spray-drying or to kneading respectively.

Water-soluble cyclodextrins which may be used according to the present invention are unsubstituted or substituted α, β or γ-cyclodextrins or hydrates thereof, preferably unsubstitued β-cyclodextrins.

The resulting forms of nimesulide with water-soluble cyclodextrins show a great improvement of dissolution and wettability properties of nimesulide in aqueous or biological media, due to the following factors:

- amorphous state of the obtained product;
- surfactant-like properties of cyclodextrins which can reduce the interfacial tension between water-insoluble drugs and the solvent;
- the smaller particle size produced by the co-milling, spray-drying and kneading processes;
- reduction of the dissolution energy of nimesulide

brought by its complete or partial amorphization or by the transition of its original crystalline state into a higher energy state.

The methods of the invention show furthermore a significant versatility over the other known methods. They offer, in particular, an one-step process with the advantage of reducing the preparation steps saving time and cost, as well as better process control.

Also, the micromeritic properties of the spray-dried, co-milled and kneaded products can be checked in order to facilitate the next formulation steps, necessary for the preparation of the conventional solid oral dosage form, as granules, capsules, tablets.

The method, according to the present invention, involves a particularly simply and safe procedure and it is generally applicable in the preparation of other complexes of cyclodextrins with different drugs.

The different realization forms, according to the method of the invention, are now described in detail:

a. **Co-milling**

A dry mixture of nimesulide and water-soluble cyclodextrins is laced in a rotating ball mill, in a vibrational ball mill, in an automatic rotor speed mill or any other suitable comminution, crushing, milling, micronization apparatus until an amorphization of the crystalline nimesulide is achieved. The amorphization degree is checked by the absence in the Differential Scanning Calorimetry thermogram of the obtained compound of the endothermic peak relative to the solid/liquid transition of the crystalline nimesulide. The milling of the inclusion compound can be stopped

when an amorphization degree of nimesulide (measured by the reduction of enthalpy value of melting of the crystalline nimesulide) sufficient to sensibly increase the dissolution rate, is achieved.

Molar ratios between nimesulide and water-soluble cyclodextrins, in the mixture to be milled can vary from 1 : 0.5 and 1 : 10 moles/moles respectively, preferably between 1 : 0.8 and 1 : 4 moles/moles. The resulting milled mixture can be forced through a sieve to eliminate possible aggregates and then mixed in any mixing device to guarantee the most homogeneity and fluidity of the product. The resulting powdered milled inclusion compound of nimesulide and cyclodextrins can be subsequently used to prepare any desired solid dosage form (granules, tablets, capsules) with or without the addition of any excipients conventionally used in the pharmaceutical compositions.

b. Spray-drying

Nimesulide and water-soluble cyclodextrins are co-mixed in distilled water and the pH of the solution is adjusted to the desired value by adding 0.1 NaOH or NH_4OH.

The solutions and the homogeneous suspensions are atomized into a drying chamber with a spray nozzle. The spray atomized typically works under the following conditions:

inlet temperature:	140°C
outlet temperature:	70°C
drying air flow rate:	0.35 m^3/min
atomizing air pressure:	1 Kg./cm^2
liquid phase feeding speed:	4 ml/min.

Molar ratios between nimesulide and water-soluble cyclodextrins in the preparation of their alkaline solution can vary from 1 : 0.5 and 1 : 10 moles/moles respectively, preferably between 1 : 0.8 and 1 : 4 moles/moles. The resulting mixture can be forced through a sieve to eliminate possible aggregates and subsequently mixed in any mixing device to guarantee the most homogeneity and fluidity of the product. The resulting powdered inclusion compound of nimesulide and cyclodextrins can be subsequently used to prepare any desired solid dosage form (granules, tablets, capsules) with or without the addition of any excipients of common use in the pharmaceutical compositions.

c. Kneading

Nimesulide is solubilized or suspended in an alkaline aqueous solution (pH > 7.0) and then water-soluble cyclodextrins are added. The preparation is homogenized by mixer-homogenizer, like Silverson, for the time period needed to achieve the desired degree of amorphization of the crystalline nimesulide. The preparation is dried in a forced ventilation oven at 40-50°C overnight.

Molar ratios between nimesulide and water-soluble cyclodextrins in the preparation of their alkaline aqueous solution can vary from 1 : 0.5 and 1 : 10 moles/moles respectively, preferably between 1 : 0.8 and 1 : 4 moles/moles. The resulting mixture can be forced through a sieve to eliminate possible aggregates and subsequently mixed in any mixing device to guarantee the most homogeneity and fluidity of the product. The resulting powdered inclusion compound of

nimesulide and cyclodextrins can be subsequently used to prepare any desired solid dosage form (granules, tablets, capsules) with or without the addition of any of the common excipients used in the pharmaceutical compositions.

The following examples illustrate the invention:

Example 1

Nimesulide (200 g) and the suitable amount of ß-cyclodextrin (about 205 g) were dry-mixed and then milled by a rotating ball mill. This working, being in function with the capacity and potency of the mill, can be repeated more time until nimesulide-ß-cyclodextrin compound of the desired crystallinety was obtained. Yield : 95%. After milling the compound was again mixed and forced through a 0.038 mm sieve to guarantee the homogeneity and to eliminate possible aggregates before using it for the formulations.

Example 2

210 g of nimesulide were partially solubilized in 800 ml of ammoniacal solution (pH 8.2). The obtained suspension was homogenized and dispersed by means of a mixer-homogenizer like Silverson for 2 hours. The suitable amount of ß-cyclodextrin was added in order to obtain a nimesulide-ß-cyclodextrin compound 1 : 2. After dispersion, ß-cyclodextrins were solubilized under stirring by Silverson until the suspension homogenization and solid particle reduction were achieved. The compound was dried in an oven at 45°C overnight putting it in a thin layer. Before sending the compound for the formulations, it was milled by a 200 µm sieve.

Example 3

Nimesulide was dissolved in alkaline solution (5 l/for the addition of NH_4OH (pH 8.2). The required amount of ß-cyclodextrin was then added to the alkaline solution on ß-cyclodextrin, in order to have a molar ratio 1 : 1 in the final compound. The mixture was kept under stirring until a complete dissolution. The solution was feeded (spray-drier BUCUI 190 M) with the following operative conditions:

feeding speed:	720 ml/h
air temperature:	150°C
air flow:	400 l/h

Example 4

Granules

Inclusion compound of nimesulide with ß-cyclodextrins	468 mg
sorbitol	2472 mg
Saccharin sodium	10 mg
Orange flavour powder	50 mg

Characteristics of inclusion compound of nimesulide with cyclodextrins

1. Differential scanning calorimetry data

The differential scanning calorimetry data (using Mettler TA 3000 at a rate of 10°C/min. under N_2 gas in the range of heating temperature from 30° to 200°C) are shown in figure 1. By comparing these data with differential scanning calorimetry of pure nimesulide (a), it is possible to observe a complete amorphization in the case of kneaded mixture (c) and spray-dried one (d), and a partial amorphization for the co-milled one (b).

2. Infrared spectroscopy

The infrared spectra are reported in figure 2. By comparing the spectrum of nimesulide (a) with that of spry-dried (b), kneaded (c) and co-milled (d) there are evident modifications in the bands around 1520 cm^{-1}, due to the asymmetric stretching of nitro group, and especially in the region 1300-1200 cm^{-1}, giving proof of the significant differences existing between nimesulide and the above mentioned mixture.

3. Solubility data

The solubility (saturation concentration) of the inclusion compound of nimesulide with cyclodextrins was measured by placing an excess amount of the powdered compound in a flask containing 50 ml of pH 7.4 phosphate buffer at 25°C; the flasks were placed in a shaking apparatus and aliquots of sample solutions were taken and filtered through a Millipore membrane filter; the concentration of nimesulide in the filtered aliquot was determined by spectrophotometer VARIAM DMS 100 at 369.9 nm.

As shown in table 1, a relevant increase of the nimesulide solubility values was achieved by preparing the inclusion compound of nimesulide and cyclodextrins, according to the present invention. It is particularly interesting to observe that nimesulide concentrations resulting from the inclusion compound of nimesulide with cyclodextrins are about 20 times higher than from crystalline pure nimesulide.

4. Dissolution data

Dissolution profiles of the inclusion compound of nimesulide with cyclodextrins were measured applying

the USP XXII dissolution method. The withdrawn sample solutions are checked for the nimesulide concentration by UV.Vis spectrophotometric analysis. These results stress the advantages of the inclusion compound of nimesulide with cyclodextrins obtained by any of the three techniques (table 2), described in this application.

TABLE I

EQUILIBRIUM SOLUBILITY

NIMESULIDE	0.032	mg/ml
SPRAY-DRIED	0.61	mg/ml
CO-MILLED	0.57	mg/ml
KNEADED	0.61	mg/ml

TABLE II

DISSOLUTION KINETICS

PRODUCT	10 min	20 min	30 min	60 min	90 min	120 min
NIMESULIDE	4.2%	10.4%	15.3%	18.8%	21.7%	28.4%
CO-MILLED	41.6%	60.7%	60.6%	60.2%	60.9	61.8%
SPRAY-DRIED	47.6%	58.2%	60.8%	64.4%	63.1%	61.9%
KNEADED	48.2%	59.1%	61.2%	62.7%	62.9%	62.8%

CLAIMS

1. A method for the preparation of the inclusion compounds of nimesulide with cyclodextrins which consists in subjecting a solid mixture, an aqueous solution or a homogeneous slurry of nimesulide and water-soluble cyclodextrins to co-milling, to spray-drying or to kneading respectively.

2. A method according to claim 1, in which the molar ratio of nimesulide to water-soluble cyclodextrins is comprised between 1 : 0.5 and 1 : 10.

3. A method according to claims 1 or 2, in which the water-soluble cyclodextrins are selected from unsubstituted, substituted α, β and γ-cyclodextrins, or a hydrates thereof.

4. A method according to claim 3 in which the water-soluble cyclodextrin is the unsubstituted β-cyclodextrin.

FIGURE 1

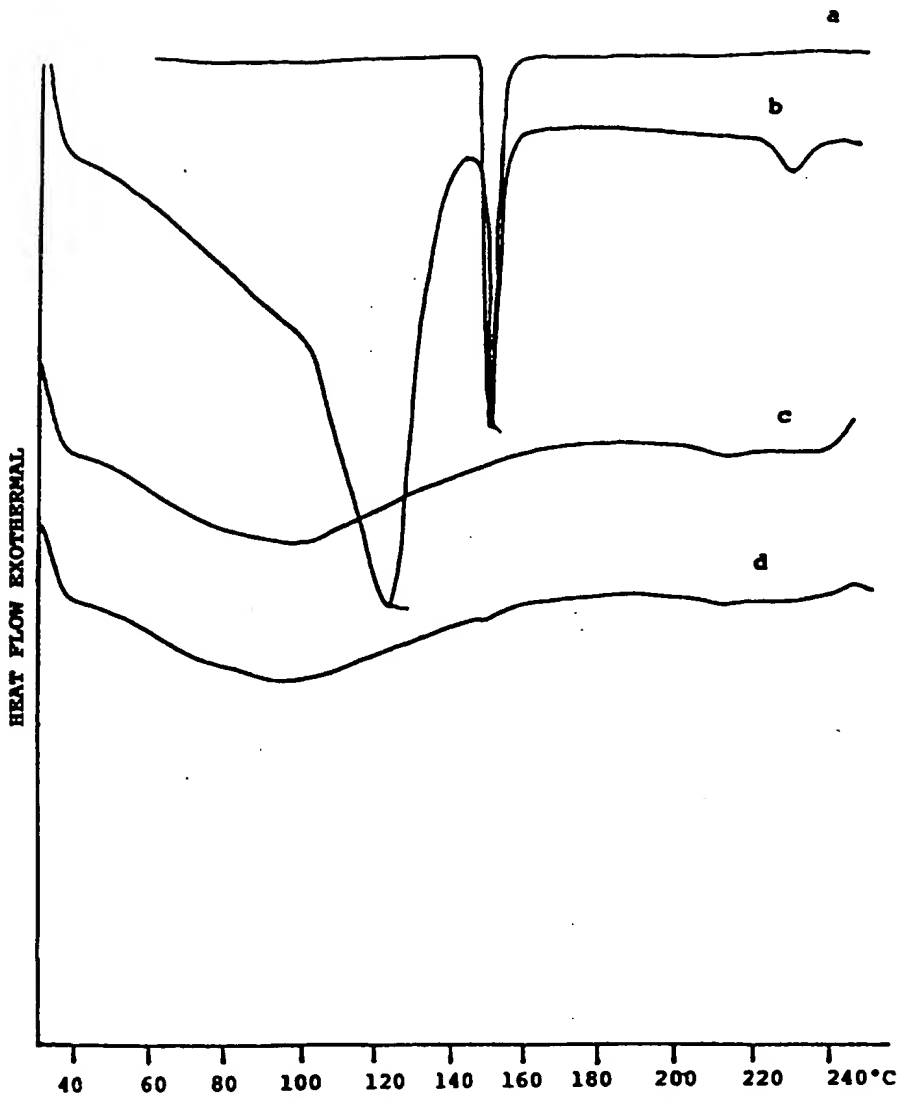
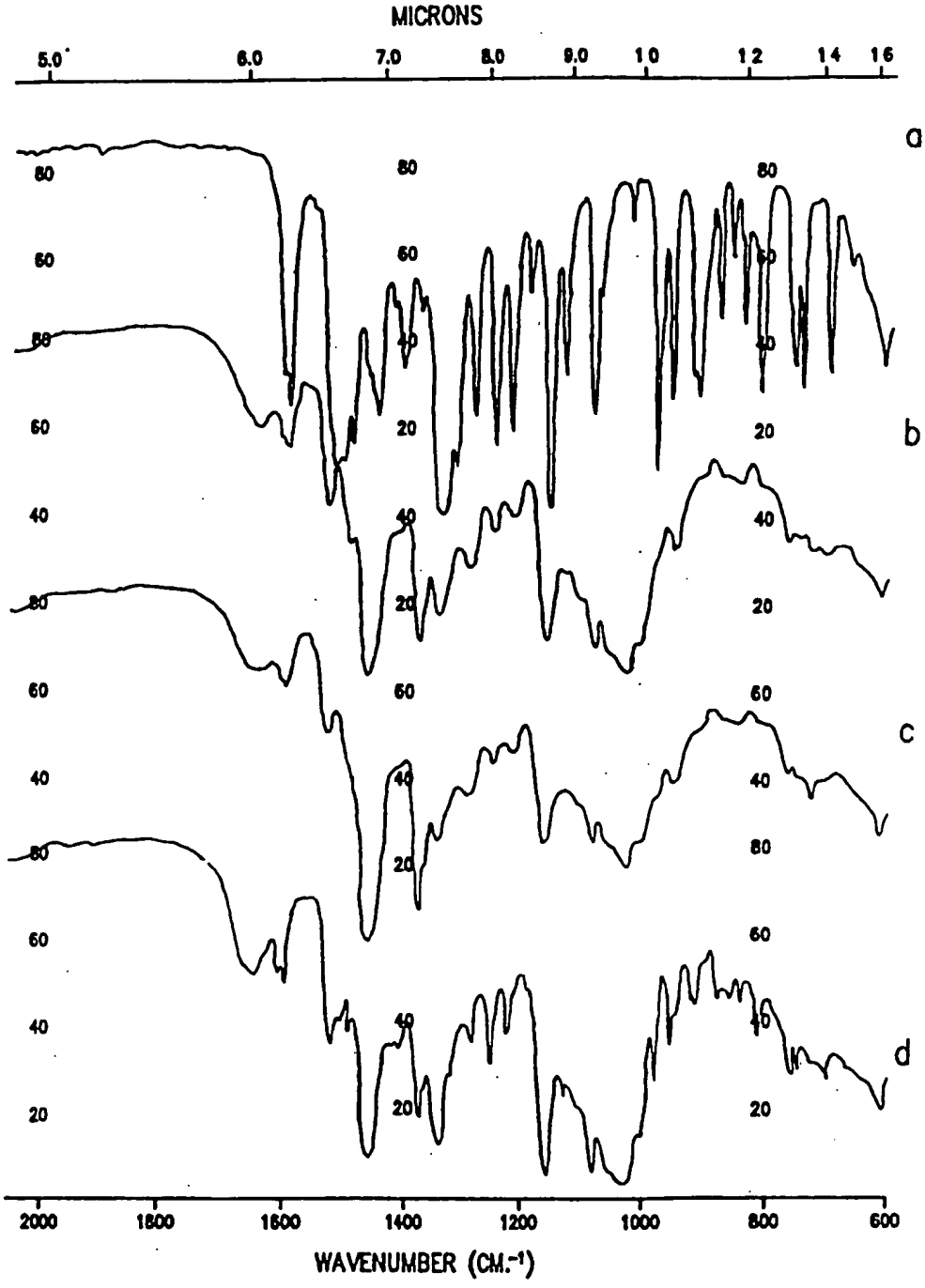

a
b
c
d
HEAT FLOW EXOTHERMAL
40
60
80
100
120
140
160
180
200
220
240°C

FIGURE 2



SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/EP 93/01560

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K47/48 A61K31/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO,A,91 17774 (BOEHRINGER INGELHEIM ITALIA S.P.A.) 28 November 1991 cited in the application see page 2, paragraph 2 -paragraph 3; claims; example 4 ---	1-4
X,Y	FR,A,2 662 360 (LEETRIM LTD) 29 November 1991 see claims; examples --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 118, no. 22, 1992, Columbus, Ohio, US; abstract no. 219627y, see abstract & CONGR. INT. TECHNOL. PHARM. 6TH vol. 5 pages 339 - 348 L. OWAIS ET AL. 'A NOVEL METHOD FOR THE PREPARATION OF SOME BETA CYCLODEXTRIN COMPLEXES USING A COLLOIDAL MILL.' ---	1-4
Y	EP,A,0 371 431 (VECTORPHARMA INTERNATIONAL) 6 June 1990 see claims 1,11 -----	1-4

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. nal Application No
PCT/EP 93/01560

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